Migraine and Risk of Cardiovascular Disease in Women

Tobias Kurth, MD, ScD
J. Michael Gaziano, MD, MPH
Nancy R. Cook, ScD
Giancarlo Logroscino, MD, PhD
Hans-Christoph Diener, MD, PhD
Julie E. Buring, ScD

Context Migraine with aura has been associated with an adverse cardiovascular risk profile and prothrombotic factors that, along with migraine-specific physiology, may increase the risk of vascular events. Although migraine with aura has been associated with increased risk of ischemic stroke, an association with cardiovascular disease (CVD) and, specifically, coronary events remains unclear.

Objective To evaluate the association between migraine with and without aura and subsequent risk of overall and specific CVD.

Design, Setting, and Participants Prospective cohort study of 27 840 US women aged 45 years or older who were participating in the Women's Health Study, were free of CVD and angina at study entry (1992-1995), and who had information on self-reported migraine and aura status, and lipid measurements. This report is based on follow-up data through March 31, 2004.

Main Outcome Measures The primary outcome measure was the combined end point of major CVD (first instance of nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic CVD); other measures were first ischemic stroke, myocardial infarction, coronary revascularization, angina, and death due to ischemic CVD.

Results At baseline, 5125 women (18.4%) reported any history of migraine; of the 3610 with active migraine (migraine in the prior year), 1434 (39.7%) indicated aura symptoms. During a mean of 10 years of follow-up, 580 major CVD events occurred. Compared with women with no migraine history, women who reported active migraine with aura had multivariable-adjusted hazard ratios of 2.15 (95% confidence interval [CI], 1.58-2.92; $P<.001$) for major CVD, 1.91 (95% CI, 1.17-3.10; $P=.01$) for ischemic stroke, 2.08 (95% CI, 1.30-3.31; $P=.002$) for myocardial infarction, 1.74 (95% CI, 1.23-2.46; $P=.002$) for coronary revascularization, 1.71 (95% CI, 1.16-2.53; $P=.007$) for angina, and 2.33 (95% CI, 1.21-4.51; $P=.01$) for ischemic CVD death. After adjusting for age, there were 18 additional major CVD events attributable to migraine with aura per 10 000 women per year. Women who reported active migraine without aura did not have increased risk of any vascular events or angina.

Conclusions In this large, prospective cohort of women, active migraine with aura was associated with increased risk of major CVD, myocardial infarction, ischemic stroke, and death due to ischemic CVD, as well as with coronary revascularization and angina. Active migraine without aura was not associated with increased risk of any CVD event.

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MIGRAINE IS A COMMON, primary, chronic-intermittent neurovascular headache disorder characterized by episodic severe headache accompanied by autonomic nervous system dysfunction and, in some patients, transient neurologic symptoms known as migraine aura.[1,2] In the United States, the 1-year prevalence of migraine is approximately 18% in women and 6% in men; an estimated 28 million Americans have severe and disabling migraines.[3]

Migraine-specific neurovascular dysfunctions[4,5] and the elevated frequency of ischemic stroke among young women with migraine[6] have led to speculation that migraine may be a risk factor for ischemic stroke. Indeed, several studies have found associations between migraine, especially migraine with aura, and increased risk of ischemic stroke.[7-10] Since some studies have suggested that migraine, particularly migraine with aura, is associated with an unfavorable cardiovascular risk profile[11] and prothrombotic or vasoactive factors,[12-16] and since the vascular dysfunction of migraine may also extend to coronary arteries,[17,18] it is plausible that migraine, and especially mi-

For editorial comment see p 332.

Author Affiliations: Divisions of Preventive Medicine (Drs Kurth, Gaziano, Cook, and Buring) and Aging (Drs Kurth, Gaziano, Logroscino, and Buring), Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Department of Epidemiology, Harvard School of Public Health (Drs Kurth, Cook, Logroscino, and Buring), Massachusetts Veterans Epidemiology Research and Information Center, Boston VA Healthcare System (Dr Gaziano), and Department of Ambulatory Care and Prevention, Harvard Medical School (Dr Buring), Boston, Mass; and Department of Neurology, University of Duisburg-Essen, Essen, Germany (Dr Diener).
Corresponding Author: Tobias Kurth, MD, ScD, Division of Preventive Medicine, Brigham and Women's Hospital, 900 Commonwealth Ave E, Boston, MA 02215-1204 (tkurth@rics.bwh.harvard.edu).

graine with aura, may be associated with other vascular events, not just ischemic stroke. Although an association between migraine and chest pain has been described,[19,20] an association between migraine and coronary events has not been firmly established.[21] In a previous report from the Women's Health Study (WHS), migraine was not associated with coronary heart disease after a mean of 6 years of follow-up.[22] However, the number of outcome events was too small to conclusively assess the association between migraine with aura and coronary heart disease.

We thus evaluated the association between migraine with or without aura and subsequent risk of overall and specific ischemic vascular events in the WHS, a large, prospective cohort of apparently healthy women, during a mean of 10 years of follow-up.

METHODS

Study Population

The WHS was a randomized, placebo-controlled trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease (CVD) and cancer among apparently healthy women. The design, methods, and results have been described in detail previously.[23-25] Briefly, a total of 39 876 US female health care professionals aged 45 years or older at study entry (1992-1995) without a history of CVD, cancer, or other major illnesses were randomly assigned to receive active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. All participants provided written informed consent, and the institutional review board of Brigham and Women's Hospital, Boston, Mass, approved the WHS. Baseline information was self-reported and collected by a mailed questionnaire that asked about many cardiovascular risk factors and lifestyle variables. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes and other information during the study period. For this analysis, we included follow-up information from the time of randomization through March 31, 2004. As of this date, morbidity follow-up was 97.2% complete and mortality follow-up was 99.4% complete.

Blood samples were collected in tubes containing EDTA from 28 345 participating women prior to randomization. A total of 27 939 samples could be assayed for total, high-density lipoprotein, and directly obtained low-density lipoprotein cholesterol with the use of reagents from Roche Diagnostics (Basel, Switzerland) and Genzyme (Cambridge, Mass). Of these, we excluded 79 women with missing migraine information and 20 who reported angina prior to study entry, leaving 27 840 women free of CVD or angina at baseline for this study.

Assessment of Migraine

The baseline questionnaire elicited detailed information about migraine. Participants were asked, "Have you ever had a migraine headache?" and "In the past year, have you had a migraine headache?" We defined 3 main categories: (1) no migraine history; (2) active migraine, which includes women with self-reported migraine in the year prior to completing the baseline questionnaire; and (3) prior migraine, which includes women who reported ever having had a migraine but none in the year prior to completing the questionnaire. Participants who reported active migraine were asked details about their migraine attacks, including attack duration of 4 to 72 hours, unilateral location of pain, pulsating quality, inhibition of daily activities, aggravation by routine physical activity, sensitivity to light, sensitivity to sound, and nausea or vomiting. This information allowed us to classify women based on modified 1988 International Headache Society (IHS) criteria for migraine.[26] Of the women who reported active migraine, 46.6% fulfilled all modified IHS criteria for migraine (code 1.1) and 83.5% fulfilled all but 1 modified IHS criteria (code 1.7, migrainous disorder). Participants who reported active migraine were further asked whether they had an "aura or any indication a migraine is coming." Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura, similar to previous studies.[8,22] However, we did not have further details to classify migraine aura based on IHS definitions. To more directly compare our results with those of other studies, we also created a fourth category, "any history of migraine," that included women who reported active migraine and prior migraine.

Outcome Ascertainment

During follow-up, participants self-reported cardiovascular events, coronary revascularization, and angina. Medical records were obtained for all cardiovascular events and coronary revascularizations, but not angina, and reviewed by an end points committee of physicians. Nonfatal stroke was confirmed if the participant had a new focal-neurologic deficit of sudden onset that persisted for more than 24 hours and classified into its major subtypes based on available clinical and diagnostic information with excellent interrater agreement.[27] The occurrence of myocardial infarction was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or diagnostic electrocardiogram results. Cardiovascular deaths were confirmed by review of autopsy reports, death certificates, medical records, or information obtained from next of kin or family members.

The primary outcome was major CVD, a combined end point defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic CVD. We also evaluated the association between migraine and any first ischemic stroke, myocardial infarction, coronary revascularization, angina, and death due to ischemic CVD.

Statistical Analyses

We compared the baseline characteristics of participants with respect to

their migraine status using the general linear models procedure (SAS statistical software, version 9.1, SAS Institute Inc, Cary, NC) for continuous measurements, adjusting for age. We used direct standardization to adjust categorical variables and incidence rates of CVD for age in 5-year increments.

We used Cox proportional hazards models to evaluate the association between migraine status and the various outcomes. We calculated age- and multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs). The multivariable model controlled for age (continuous), systolic blood pressure categories (10–mm Hg increments), antihypertensive medication use (yes or no), history of diabetes (yes or no), body mass index (<25, 25-29.9, or ≥30; calculated as weight in kilograms divided by height in meters squared), smoking (never, past, current [<15 cigarettes/d], or current [≥15 cigarettes/d]), alcohol consumption (rarely/never, 1-3 drinks/mo, 1-6 drinks/wk, or ≥1 drinks/d), exercise (rarely/never, less than once a week, 1-3 times a week, or ≥4 times a week), postmenopausal status, postmenopausal hormone use (never, past, or current), history of oral contraceptive use (yes or no), family history of myocardial infarction prior to age 60 years (yes or no), low- and high-density lipoprotein plasma levels (quartiles), cholesterol-lowering medication use (yes or no), as well as randomized treatment assignments. We incorporated a missing value indicator in the outcome models if the number of women with missing information was 100 or more and imputed a value otherwise.

We tested the proportionality assumption of the Cox proportional hazards models by including an interaction term for migraine status with the logarithm of time and found no statistically significant violation.

We evaluated effect modification by age (<50, 50-59, or ≥60 years), history of hypertension (yes or no), smoking status (never, past, or current), total cholesterol level (<200, 200-239, or ≥240 mg/dL [<5.17, 5.17-6.20, or ≥6.21 mmol/L]), history of oral contraceptive use (yes or no), and current postmenopausal hormone use (yes or no). We assessed statistical significance of effect modification by adding a multiplicative term for dichotomous variables to the models, and used a trend test across the mean values of categorical variables. All *P* values were 2-tailed, and $P<.05$ was considered statistically significant.

RESULTS

Of the 27 840 participants, 5125 (18.4%) reported any history of migraine. Of the 3610 women with active migraine, 1434 (39.7%) reported aura. **TABLE 1** summarizes the women's age-adjusted baseline characteristics according to migraine status. Compared with women with no migraine history, women with active migraine with aura had a more unfavorable cholesterol profile and were less likely to currently smoke cigarettes, to regularly consume alcohol, and to regularly exercise. They were less likely to be premenopausal but more likely to currently use postmenopausal hormones or to have a history of oral contraceptive use and were more likely to report a family history of myocardial infarction prior to age 60 years. The most adverse cardiovascular risk profile, however, was recorded for women who indicated prior migraine—they were older, had unfavorable cholesterol levels, and were more likely to be hypertensive or obese or to currently smoke cigarettes.

During a mean of 10 years of follow-up (278 086 person-years), we confirmed 580 first major CVD events, 251 ischemic strokes, 249 myocardial infarctions, and 130 ischemic CVD deaths. In addition, 514 coronary revascularizations and 408 cases of angina occurred. In **TABLE 2**, we report the age-adjusted incidence rates of the outcome events per 10 000 women per year according to migraine status. Compared with women with no migraine history, the incidence rates of all outcome events were increased among women who reported active migraine with aura. After adjusting for age, there were 18 additional major CVD events attributable to migraine with aura per 10 000 women per year. Women with prior migraine had increased incidence rates specifically for coronary revascularization and angina. In contrast, women with active migraine without aura had incidence rates similar to women with no migraine history.

TABLE 3 summarizes the age- and multivariable-adjusted associations between migraine status and the various vascular events. Compared with women with no migraine history, women who reported any history of migraine were at increased risk of all evaluated ischemic vascular outcomes, with the exception of ischemic stroke. The increased risk of CVD was strikingly different according to migraine aura status. Compared with women with no migraine history, women who reported active migraine with aura had multivariable-adjusted HRs of 2.15 (95% CI, 1.58-2.92; $P<.001$) for major CVD, 1.91 (95% CI, 1.17-3.10; $P=.01$) for ischemic stroke, 2.08 (95% CI, 1.30-3.31; $P=.002$) for myocardial infarction, 1.74 (95% CI, 1.23-2.46; $P=.002$) for coronary revascularization, 1.71 (95% CI, 1.16-2.53; $P=.007$) for angina, and 2.33 (95% CI, 1.21-4.51; $P=.01$) for ischemic CVD death. Women who reported prior migraine had significantly increased risk of coronary revascularization and angina. Women who reported active migraine without aura did not have significantly increased risks of any CVD event or angina compared with women without migraine history.

FIGURE 1 shows the age-adjusted cumulative incidence of major CVD and **FIGURE 2** shows the age-adjusted cumulative incidence of specific CVD for women with no migraine, active migraine with aura, and active migraine without aura. The curves diverge after a mean follow-up of approximately 6 years, showing increased risks of all evaluated outcomes for women who reported active migraine with aura. The incidence rates of CVD death showed a similar pattern (data not shown).

The association between active migraine with aura and major CVD was not significantly modified by age or total cholesterol levels. The association between active migraine with aura and ischemic stroke was significantly modified by age ($P = .01$) and marginally significantly modified by total cholesterol levels ($P = .06$), with the highest association among women younger than 50 years (HR, 6.16; 95% CI, 2.34-16.21) and women with total cholesterol levels of less than 200 mg/dL (<5.17 mmol/L) (HR, 3.80; 95% CI, 1.85-7.80). In contrast, the association between active migraine with aura and myocardial infarction was not significantly modified by age or cholesterol levels and remained elevated among women aged 60 years or older (HR, 1.95; 95% CI, 0.91-4.19) and those with cholesterol levels of 240 mg/dL or higher (≥6.21 mmol/L) (HR, 2.80; 95% CI, 1.48-5.30). The association between active migraine with aura and major CVD, ischemic stroke, or myocardial infarction was not statistically significantly modified by smoking status, history of hypertension, or use of oral contraceptives or postmenopausal hormone therapy. The association between active migraine without aura and any outcome event was not

Table 1. Age-Adjusted Baseline Characteristics According to Migraine Status in the Women's Health Study (N = 27 840)*

Characteristics	No Migraine History (n = 22 715)	Active Migraine With Aura (n = 1434)	Active Migraine Without Aura (n = 2176)	Prior Migraine (n = 1515)†	*P* Value‡
Age, mean (SE), y	54.9 (0.05)	53.2 (0.16)	52.6 (0.12)	55.5 (0.18)	<.001
Body mass index§					
Mean (SE)	25.9 (0.03)	25.8 (0.13)	26.2 (0.11)	26.1 (0.13)	.02
≥30	17.4	16.1	18.6	19.4	.01
Cholesterol, mean (SE), mg/dL					
Total	211.4 (0.27)	213.4 (1.08)	212.8 (0.88)	214.8 (1.05)	.003
LDL-C	123.9 (0.22)	124.6 (0.89)	124.7 (0.73)	127.1 (0.87)	.003
HDL-C	53.9 (0.10)	53.1 (0.40)	53.2 (0.32)	52.6 (0.39)	.001
Blood pressure, mean (SE), mm Hg					
Systolic	123.6 (0.09)	123.5 (0.35)	124.4 (0.29)	124.6 (0.34)	.002
Diastolic	76.7 (0.06)	76.7 (0.24)	77.8 (0.19)	77.8 (0.23)	<.001
History of hypertension‖	24.6	25.5	26.0	30.3	<.001
Antihypertensive treatment	12.9	13.9	14.3	17.1	<.001
Cholesterol-lowering medications	3.1	3.6	3.7	3.0	.52
History of diabetes	2.5	1.8	1.6	2.6	.22
Smoking					
Never	51.3	52.7	56.3	50.6	.06
Past	37.1	37.3	34.5	35.4	
Current, <15 cigarettes/d	4.4	3.9	3.5	5.2	
Current, ≥15 cigarettes/d	7.3	6.2	5.8	8.8	
Alcohol consumption					
Rarely/never	43.5	48.4	47.4	45.0	<.001
1-3 drinks/mo	13.1	13.1	15.4	14.2	
1-6 drinks/wk	32.7	30.2	30.1	30.5	
≥1 drink/d	10.8	8.3	7.1	10.3	
Physical activity					
Rarely/never	37.0	38.3	39.4	39.2	<.001
<Once per week	19.2	20.4	21.7	20.1	
1-3 times per week	32.3	30.7	29.2	29.5	
≥4 times per week	11.6	10.7	9.7	11.3	
Premenopausal	28.1	23.9	26.2	25.1	<.001
Postmenopausal hormone therapy					
Never	49.6	39.0	44.8	46.0	<.001
Past	8.7	10.1	8.5	10.4	
Current	41.7	50.9	46.7	43.6	
History of oral contraceptive use	69.1	72.3	71.4	71.8	.001
Family history of myocardial infarction prior to age 60 y	12.6	14.3	13.0	13.8	.14

SI conversions: To convert total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) to mmol/L, multiply by 0.0259.
*Data are expressed as age-adjusted percentages unless otherwise specified. Percentages may not add to 100% because of rounding or missing values.
†Women who indicated a history of migraine but no active migraine in the previous year.
‡*P* values were calculated from 3 *df* tests of general linear models for continuous variables and Mantel-Haenszel χ^2 tests for categorical variables.
§Body mass index was calculated as weight in kilograms divided by height in meters squared.
‖Hypertension was defined as systolic blood pressure of at least 140 mm Hg, diastolic blood pressure of at least 90 mm Hg, or self-reported physician-diagnosed hypertension.

statistically significantly modified by any of the evaluated factors.

COMMENT

In this large, prospective study of initially apparently healthy women aged 45 years or older, any history of migraine was associated with increased risk of major CVD. This increased risk was strikingly different according to aura status. Compared with no migraine history, active migraine with aura was associated with a significantly increased risk of subsequent major cardiovascular events, ischemic stroke, myocardial infarction, coronary revascularization, angina, and death due to ischemic CVD after a mean follow-up of 10 years. These increased risks, which remained after adjusting for a large number of cardiovascular risk factors, ranged from a 1.7-fold increase for coronary revascularization to a 2.3-fold increase for cardiovascular death. Women with prior

Table 2. Age-Adjusted Incidence Rates of Ischemic Vascular Events per 10 000 Women per Year According to Migraine Status in the Women's Health Study (N = 27 840)

		Age-Adjusted Incidence Rate				
Ischemic Vascular Events	No. of Events	No Migraine History (n = 22 715)	Active Migraine With Aura (n = 1434)	Active Migraine Without Aura (n = 2176)	Prior Migraine (n = 1515)*	*P* Value†
Major cardiovascular event‡	580	20.0	38.3	22.6	24.8	<.001
Ischemic stroke	251	8.8	13.1	10.7	7.1	.07
Myocardial infarction	249	8.5	16.7	8.3	11.0	.02
Coronary revascularization§	514	17.7	30.3	17.1	28.8	<.001
Angina	408	13.7	23.1	13.6	25.6	<.001
Death due to cardiovascular disease	130	4.4	9.5	4.3	7.9	.05

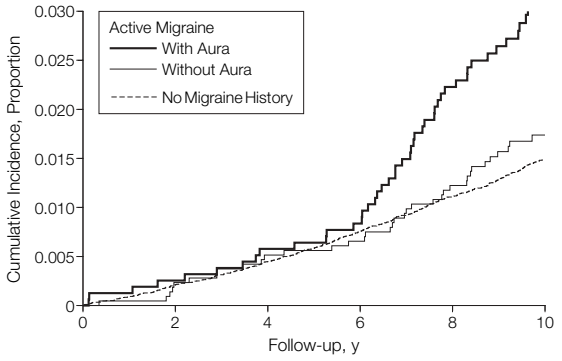
*Women who indicated a history of migraine but no active migraine in the previous year.
†*P* values were calculated from 3 *df* log-rank tests.
‡A major cardiovascular event was defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic cardiovascular cause.
§Includes reports of coronary artery bypass graft surgery or percutaneous coronary angioplasty.

Table 3. Age- and Multivariable-Adjusted Hazard Ratios for Ischemic Vascular Events According to Migraine Status in the Women's Health Study (N = 27 840)

	Hazard Ratio (95% Confidence Interval)								
Ischemic Vascular Event	No Migraine History (n = 22 715)	Any History of Migraine (n = 5125)*	*P* Value	Active Migraine With Aura (n = 1434)	*P* Value	Active Migraine Without Aura (n = 2176)	*P* Value	Prior Migraine (n = 1515)†	*P* Value
Major cardiovascular event‡	n = 458	n = 122		n = 46		n = 37		n = 39	
Age-adjusted	1.00	1.42 (1.16-1.73)	<.001	2.05 (1.51-2.78)	<.001	1.18 (0.84-1.65)	.35	1.22 (0.88-1.69)	.24
Multivariable-adjusted§	1.00	1.42 (1.16-1.74)	.001	2.15 (1.58-2.92)	<.001	1.23 (0.88-1.73)	.23	1.14 (0.82-1.58)	.45
Ischemic stroke	n = 204	n = 47		n = 18		n = 17		n = 12	
Age-adjusted	1.00	1.23 (0.89-1.69)	.21	1.81 (1.11-2.93)	.02	1.23 (0.75-2.02)	.42	0.83 (0.47-1.49)	.54
Multivariable-adjusted§	1.00	1.22 (0.88-1.68)	.23	1.91 (1.17-3.10)	.01	1.27 (0.77-2.09)	.36	0.77 (0.43-1.38)	.38
Myocardial infarction	n = 196	n = 53		n = 20		n = 16		n = 17	
Age-adjusted	1.00	1.40 (1.03-1.90)	.03	2.01 (1.27-3.19)	.003	1.13 (0.68-1.89)	.63	1.24 (0.76-2.04)	.39
Multivariable-adjusted§	1.00	1.41 (1.03-1.91)	.03	2.08 (1.30-3.31)	.002	1.22 (0.73-2.05)	.45	1.14 (0.69-1.88)	.60
Coronary revascularization‖	n = 404	n = 110		n = 36		n = 30		n = 44	
Age-adjusted	1.00	1.36 (1.10-1.69)	.004	1.67 (1.19-2.36)	.003	0.95 (0.66-1.39)	.81	1.58 (1.16-2.15)	.004
Multivariable-adjusted§	1.00	1.35 (1.09-1.67)	.006	1.74 (1.23-2.46)	.002	0.98 (0.67-1.42)	.90	1.46 (1.07-2.00)	.02
Angina	n = 314	n = 94		n = 28		n = 27		n = 39	
Age-adjusted	1.00	1.49 (1.18-1.87)	<.001	1.65 (1.12-2.43)	.01	1.09 (0.74-1.62)	.66	1.80 (1.29-2.51)	<.001
Multivariable-adjusted§	1.00	1.47 (1.17-1.86)	.001	1.71 (1.16-2.53)	.007	1.12 (0.75-1.66)	.58	1.66 (1.19-2.32)	.003
Death due to cardiovascular disease	n = 102	n = 28		n = 10		n = 6		n = 12	
Age-adjusted	1.00	1.55 (1.02-2.36)	.04	2.15 (1.12-4.12)	.02	0.97 (0.42-2.22)	.94	1.65 (0.91-3.00)	.10
Multivariable-adjusted§	1.00	1.63 (1.07-2.50)	.02	2.33 (1.21-4.51)	.01	1.06 (0.46-2.45)	.89	1.65 (0.90-3.01)	.10

*Calculated as the sum of women with active migraine with aura, active migraine without aura, and prior migraine.
†Women who indicated a history of migraine but no active migraine in the previous year.
‡A major cardiovascular event was defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death due to ischemic cardiovascular cause.
§The multivariable models are adjusted for age, systolic blood pressure, antihypertensive medication use, history of diabetes, body mass index, smoking, alcohol consumption, exercise, postmenopausal status, postmenopausal hormone use, history of oral contraceptive use, family history of myocardial infarction prior to age 60 years, low-density and high-density lipoprotein cholesterol, cholesterol-lowering medication use, and randomized treatment assignments.
‖Includes reports of coronary artery bypass graft surgery or percutaneous coronary angioplasty.

Figure 1. Age-Adjusted Cumulative Incidence of Major CVD According to Migraine Status



No. at Risk						
Active Migraine						
With Aura	1434	1428	1415	1402	1369	836
Without Aura	2176	2168	2156	2145	2121	1329
No Migraine History	22 715	22 600	22 439	22 227	21 966	14 016

Major cardiovascular disease (CVD) was defined as the first occurrence of any of the following events: nonfatal ischemic stroke, nonfatal myocardial infarction, or ischemic CVD death. Mean (SD) of follow-up, 9.9 (1.2) years. An incidence curve is not shown for women with prior migraine (women who indicated a history of migraine but no active migraine in the previous year; n=1515).

migraine had increased risk of coronary revascularization and angina. In contrast, women who reported active migraine without aura did not have significantly increased risk for any ischemic vascular event.

While the increased risk of ischemic stroke among persons with migraine with aura has been well established,[7-10] the association between migraine with aura and overall CVD, particularly coronary heart disease, is less clear.[21] A large cohort study of more than 12 000 individuals participating in the Atherosclerosis Risk in Communities Study found significant associations between migraine and angina compared with those without a headache history; the association was consistently stronger for participants who reported aura symptoms.[20] In contrast, there was no significant association between migraine or aura classification and coronary heart disease. Several methodological differences may explain this discrepancy with our findings. These include the headache status ascertainment, which was performed after at least 6 years of follow-up and, thus, was conditional on survival, and the categorization of participants into "other headache with aura," which most likely were also migraine headaches. Interestingly, women in this category had a 1.7-fold increased risk of coronary heart disease, which, however, was not statistically significant.[20]

Two studies found associations between migraine and existing vascular events[11,28] and 2 other large studies found associations between migraine and coronary events only in subgroups—one among women with a family history of myocardial infarction[19] and the other among persons with migraine who did not have prescriptions for triptans.[29] Another study[30] and a previous report of the WHS[22] did not demonstrate associations between overall migraine and major coronary events. In the previous report from the WHS, any migraine history was not associated with increased risk of subsequent major coronary heart disease after a mean follow-up of 6 years. However, there was a suggestion of increased risk of major coronary events for women with migraine with aura (HR, 1.50; 95% CI, 0.61-3.70) compared with women without migraine. Given the findings reported here, the trend was likely not significant due to the shorter follow-up and smaller number of outcome events. With regard to mortality, a cohort study suggested a reduced risk of death among women who reported at least 1 migraine feature compared with all other women.[31] In this study, however, no aura information was available.

The biological links by which migraine may be associated with ischemic vascular events are likely to be complex; their precise mechanisms are currently unknown. Migraine has been associated with increases in prothrombotic or vasoactive factors, including prothrombin factor 1.2,[12] factor V Leiden,[13] serotonin,[14] von Willebrand factor,[32] and endothelin.[33] The release of vasoactive neuropeptides during migraine attacks that may stimulate inflammatory responses has also been implicated.[34] Some of these have been specifically associated with migraine with aura.[12-14] Furthermore, migraine, particularly migraine with aura, has been associated with the methylenetetrahydrofolate reductase C677T genotype,[15,16] which is associated with increased homocysteine levels, a risk factor for vascular events. Thus, a synergistic effect between the vascular and endothelial dysfunction of migraine and factors that increase the risk of thrombotic events can be envisioned.

Migraine with aura has also been associated with a more detrimental cardiovascular risk profile, including elevated cholesterol levels, higher blood pressure, higher likelihood of hypertension, and increased Framingham risk score for coronary heart disease.[11] Thus, it is possible that migraine with aura may be a characteristic that identifies women at increased risk of progressive atherosclerosis and subsequent vascular events. Since coronary stenoses and angina are not caused by thromboembolic events, the association between active migraine with aura and these events in our study may indirectly support this hypothesis. However, the increased risk of any evaluated vascular event remained after controlling for a large number of cardiovascular risk factors.

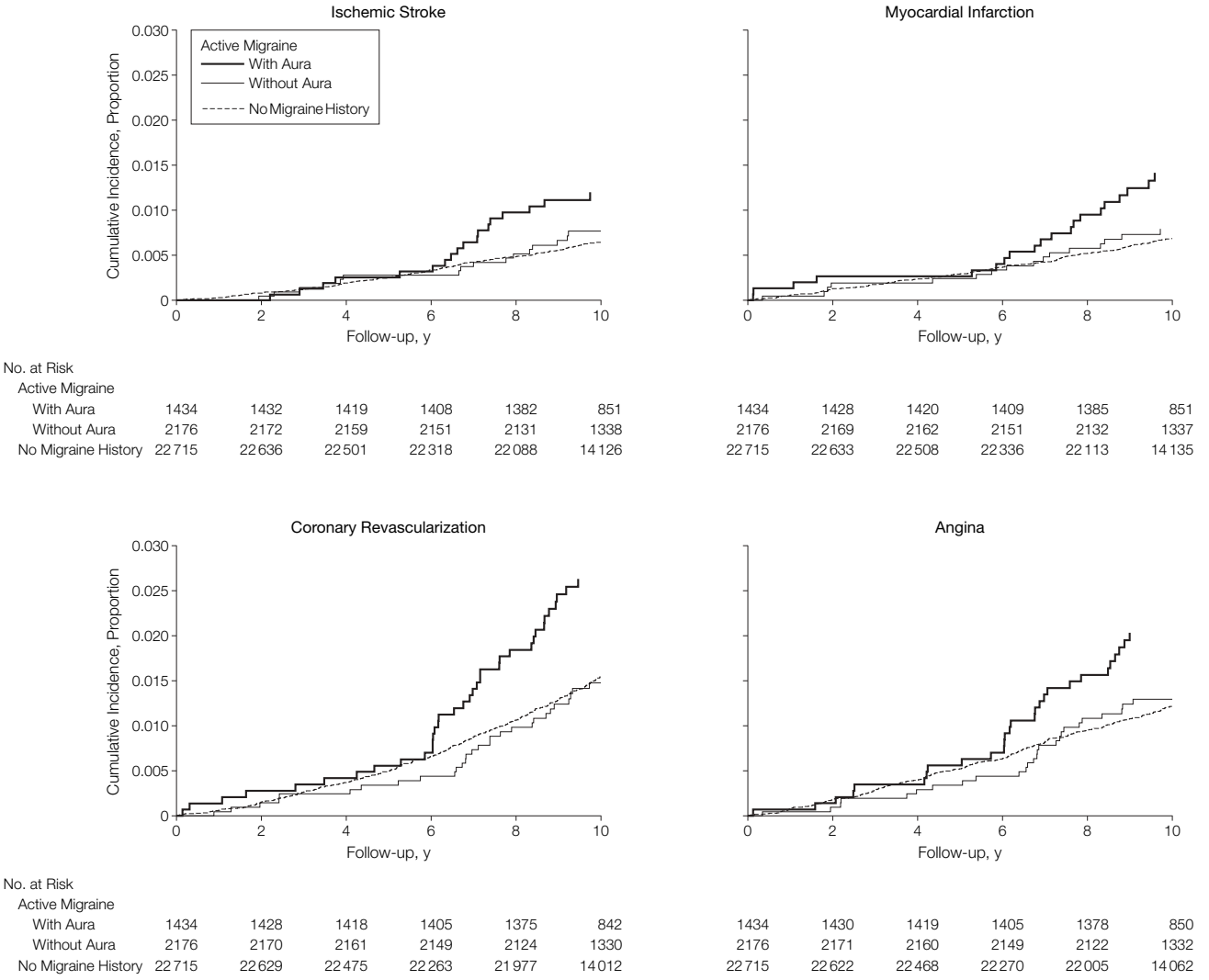
Since migraine with aura has been linked with silent brain infarctions[10] and has been described as a consequence of

a genetically determined arteriopathy,[35] a genetic component with endothelial damage may also be a plausible explanation for the increased risk of vascular events. With regard to ischemic stroke, an association between migraine with aura and congenital heart defects, particularly patent foramen ovale, has been proposed as another potential mechanism.[36] This, however, is unlikely to explain the association between migraine with aura and coronary vascular events.

The shapes of the cumulative incidence curves for all outcome events show a striking increased risk after a mean of approximately 6 years of follow-up. Potential explanations for this, however, are currently speculative and would have to involve a differential effect for migraine with aura. Aside from chance, such explanations may include the design of the WHS, underlying biological mechanisms that increase the risk of CVD only after some time period, or a change in environmental factors during follow-up.

Our study has several strengths, including a large number of participants and outcome events, high participation rate, long follow-up, prospective design, use of standardized questionnaires, and the homogenous nature of the cohort, which may reduce confounding. Furthermore, an end points committee of physicians confirmed all outcome events, with the exception of angina, after medical record review.

Figure 2. Age-Adjusted Cumulative Incidence of Ischemic Stroke, Myocardial Infarction, Coronary Revascularization, and Angina According to Migraine Status



No. at Risk

Active Migraine												
With Aura	1434	1432	1419	1408	1382	851	1434	1428	1420	1409	1385	851
Without Aura	2176	2172	2159	2151	2131	1338	2176	2169	2162	2151	2132	1337
No Migraine History	22715	22636	22501	22318	22088	14126	22715	22633	22508	22336	22113	14135

No. at Risk

Active Migraine												
With Aura	1434	1428	1418	1405	1375	842	1434	1430	1419	1405	1378	850
Without Aura	2176	2170	2161	2149	2124	1330	2176	2171	2160	2149	2122	1332
No Migraine History	22715	22629	22475	22263	21977	14012	22715	22622	22468	22270	22005	14062

Mean (SD) of follow-up for ischemic stroke, 9.9 (1.1) years; for myocardial infarction, 10.0 (1.1) years; for coronary revascularization, 9.9 (1.2) years; and for angina, 9.9 (1.2) years. Incidence curves are not shown for women with prior migraine (women who indicated a history of migraine but no active migraine in the previous year; n=1515).

Several limitations of our study should be considered. First, migraine and aura status were self-reported and were not classified according to strict IHS criteria.[26] Thus, potential nondifferential misclassification is possible; it would, however, likely yield an underestimation of the migraine-CVD association. Our migraine ascertainment allowed us to classify migraine according to modified IHS criteria.[26] In our study population, as well as in a substudy of the WHS,[37] there was consistent agreement with modified 1988 IHS criteria of migraine. In addition, we did not find significant effect modification of the association between active migraine and major CVD or individual outcomes by modified IHS classification status, nor did we find a significant association between nonmigraine headache and any CVD events (data not shown).

Second, our aura definition was broad and we had no further details to classify participants according to the IHS criteria for migraine aura. However, the aura prevalence in our study is in the range of that observed in other large population-based studies,[3,38] particularly to the 37% among women with migraine in the American Migraine Study II.[3] Furthermore, potential misclassification of self-reported aura status would likely yield an underestimation of the association between active migraine with aura and CVD events.

Third, since some aura features are difficult to distinguish from symptoms of transient ischemic attack, and since the latter is a risk factor for subsequent vascular events, particularly stroke, the association between active migraine with aura and CVD may be confounded by this mechanism. However, we believe this is an unlikely explanation, since the association between active migraine with aura and ischemic stroke is strongly apparent in younger women who have very low rates of prevalent transient ischemic attack.[39]

Fourth, we had no detailed information regarding the use of migraine-specific drugs (ie, triptans and ergot alkaloids) during the study. Because of their vasoconstrictive ability, these drugs may be associated with increased risk of vascular events. The cardiovascular safety profiles of migraine-specific drugs, however, do not support a strong association with CVD events.[29,30,40,41] In addition, since migraine-specific drugs are used by all migraine patients, not only those with aura, it seems an unlikely explanation of our findings. In the WHS, women were asked on the 48-month questionnaire to provide information regarding medication use during the previous 2 weeks. The frequency of migraine-specific drug use among women who reported active migraine at baseline was 5.3% and was not significantly different according to aura status ($P = .40$).

Fifth, although we adjusted for a large number of potential confounders, residual confounding is possible since our study design is observational. However, the striking specificity of our findings for active migraine with aura and the biological plausibility makes such an explanation unlikely.

Sixth, we had no information regarding the duration of migraine prior to study entry or migraine frequency during follow-up. However, when we updated information on active migraine during follow-up, the association between active migraine and CVD was essentially unchanged (data not shown).

Finally, participants of the WHS were all health care professionals aged 45 years or older and mostly white; thus, generalizability may be limited. We have no reason, however, to believe that that the biological mechanisms by which migraine with aura may be associated with increased risk of vascular events may be different in other female populations.

In conclusion, in this large, prospective cohort of women, active migraine with aura was associated with an increased risk of subsequent overall and specific ischemic vascular events including coronary heart disease. Women who reported active migraine without aura did not have significantly increased risks for any ischemic vascular event. Since migraine without aura is far more common than migraine with aura, our data demonstrate no increased risk of CVD for the majority of migraine patients. Future research should focus on a better understanding of the relationship between migraine, aura status, and cardiovascular events.

Author Contributions: Dr Kurth had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analyses.
Study concept and design: Kurth.
Acquisition of data: Buring.
Analysis and interpretation of data: Kurth, Gaziano, Cook, Logroscino, Diener, Buring.
Drafting of the manuscript: Kurth.
Critical revision of the manuscript for important intellectual content: Kurth, Gaziano, Cook, Logroscino, Diener, Buring.
Statistical analysis: Kurth, Cook.
Obtained funding: Buring.
Study supervision: Gaziano, Buring.
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and/or packaging from Bayer HealthCare and Natural Source Vitamin E Association; has received honoraria from Bayer for speaking engagements; and serves on an external Scientific Advisory Committee for Procter & Gamble.

We have learned that it is best to disclose all relationships with for-profit companies and allow the editor(s) to decide what is "relevant."

Tobias Kurth, MD, ScD
tkurth@rics.bwh.harvard.edu
J. Michael Gaziano, MD, MPH
Nancy R. Cook, ScD
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, Mass

Giancarlo Logroscino, MD, PhD
Department of Epidemiology
Harvard School of Public Health
Boston, Mass

Hans-Christoph Diener, MD, PhD
Department of Neurology
University of Duisburg-Essen
Essen, Germany

Julie E. Buring, ScD
Department of Medicine
Brigham and Women's Hospital
Harvard Medical School
Boston, Mass

1. Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener HC, Buring JE. Migraine and risk of cardiovascular disease in women. *JAMA*. 2006;296:283-291.
2. Flanagin A, Fontanarosa PB, DeAngelis CD. Update on *JAMA*'s conflict of interest policy. *JAMA*. 2006;296:220-221.

In Reply: The letter from Dr Kurth and colleagues is an example of how authors may misunderstand the *JAMA* policies for reporting conflicts of interest and financial disclosures[1] and why we published an updated clarification and enhanced the policies.[2] The authors believe they have no financial interests, relationships, or affiliations that would be relevant to their study describing a "biological link between migraine and cardiovascular disease." However, since the late 1980s,[3] our policy has required *complete* disclosure of all financial interests and relationships and all affiliations relevant to the subject matter discussed in the article. In this case, financial interests and relationships with manufacturers of products that are used in the management of migraine or cardiovascular disease certainly are relevant and should be disclosed, as the authors have now reported.

As recently described, *JAMA* now will require that authors include disclosure of all potential conflicts of interest in the manuscript at the time of submission.[2] Authors should always err on the side of full disclosure and should contact the editorial office if they have any questions or concerns about what constitutes a relevant financial interest or relationship. As in the past, we will continue to evaluate all cases very seriously in which authors fail to fully disclose their conflict of interest information; not only will we continue to correct the literature, but we will continue to take additional necessary action based on the results of that evaluation.

Catherine D. DeAngelis, MD, MPH
Editor in Chief, *JAMA*

Phil B. Fontanarosa, MD, MBA
Executive Deputy Editor, *JAMA*

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3. Lundberg GD, Flanagin A. New requirements for authors: signed statements of authorship responsibility and financial disclosure. *JAMA*. 1989;262:2003-2004.

CORRECTION

Unreported Financial Disclosures: In the Original Contribution entitled "Migraine and Risk of Cardiovascular Disease in Women" published in the July 19, 2006, issue of *JAMA* (2006;296:283-291), the following financial disclosures were not reported:

Dr Kurth has received investigator-initiated research grants from Bayer AG, McNeil Consumer & Specialty Pharmaceuticals, and Wyeth Consumer Healthcare; he is a consultant to i3 Drug Safety and has received an honorarium for contribution to an advisory board from Organon.

Dr Gaziano has received investigator-initiated research grants from BASF, DSM Pharmaceuticals, Wyeth Pharmaceuticals, McNeil Consumer Products, and Pliva; has received honoraria from Bayer and Pfizer for speaking engagements; and is a consultant for Bayer, McNeil Consumer Products, Wyeth Pharmaceuticals, Merck, Nutraquest, and GlaxoSmithKline.

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